Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials
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CRD summary
This review assessed the evidence base for the use of cholinesterase inhibitors in the treatment of Alzheimer's disease. The authors concluded that the research has serious methodological limitations and the clinical benefits of these drugs are small. The conclusions follow from the evidence presented, although the review addressed global benefit and did not investigate the benefit to subgroups of individuals with Alzheimer's disease.

Authors' objectives
To explore the scientific evidence for the clinical use of donepezil, rivastigmine and galantamine.

Searching
MEDLINE and EMBASE (both from 1989 to November 2004) and the Cochrane Database of Systematic Reviews were searched without any language restriction. The bibliographies of the included studies were also checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with double-blinding were eligible for inclusion.

Specific interventions included in the review
Studies of donepezil, rivastigmine or galantamine compared with placebo were eligible for inclusion. Studies of head-to-head comparisons were not included. The doses used in the included studies ranged from 1 to 10 mg for donepezil, from 1 to 12 mg for rivastigmine, and from 8 to 36 mg for galantamine. The duration of treatment ranged from 6 weeks to 3 years.

Participants included in the review
Studies of patients with Alzheimer's disease were eligible for inclusion. Studies of vascular dementia were excluded. Apart from one included study that used the American Psychiatric Association's DSM-IV diagnosis of dementia, all the studies included patients with probable or possible Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association. The baseline mean Mini-Mental State Examination score ranged from 11.7 to 21.8, though in most studies the mean was greater than 17.

Outcomes assessed in the review
All clinical outcomes were eligible. The included studies used diverse outcome measures. The most commonly used outcome measures were the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) and the clinician's interview-based impression of change scale with caregiver input (CIBIC-plus). Other measures used included the time to clinically evident functional decline and a range of other clinical scales.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The studies were assessed using a checklist of 16 criteria based on the Consolidated Standards of Reporting Trials (CONSORT) statement. Such criteria included: method of randomisation; use of blinding; intention-to-treat analysis; whether the groups were comparable at baseline; missing outcome data; missing information in the publication; whether
there was appropriate correction for multiple statistical comparisons; and whether the calculation of mean values might have biased the results. Three authors independently assessed the quality of the included studies. A consensus judgement was reached through discussion.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The mean difference between treatment and placebo on the primary end point was estimated, along with the 95% confidence interval (CI) and the associated P value, for each study. The frequency of adverse events was also estimated.

Methods of synthesis
How were the studies combined?
A narrative synthesis was conducted, with studies grouped on the basis of the outcome measure used. The three cholinesterase inhibitors were grouped together.

How were differences between studies investigated?
Differences between the studies were detailed in tables and discussed in the text.

Results of the review
Twenty-two RCTs (n=9,030) were included.

The quality assessment identified numerous methodological weaknesses in the included studies. These included a lack of correction for multiple statistical comparisons (7 studies), no intention-to-treat analysis (15 trials) and an inappropriate handling of incomplete data (8 studies).

ADAS-cog (14 trials): the mean differences between the treatment and placebo groups ranged from 1.5 to 3.9 points on the 70-point scale. Twelve of the trials showed a statistically significant difference in favour of the treatment group.

CIBIC-plus (12 trials): benefits of treatment were reported in all trials that used this outcome measure, with a statistically significant difference found between groups in favour of the treatment group. In five of these studies the difference was no longer statistically significant when the multiple statistical comparisons had been accounted for. In those studies reporting a mean difference (5 trials), the mean differences ranged from 0.26 to 0.54 points on the 7-point scale.

Other outcome measures (10 trials): the findings in this group of studies were mixed, with 5 studies showing a statistically significant benefit in favour of the treatment group. However, after correcting for multiple testing, the difference was no longer statistically significant in 2 studies. There were no differences between treatment and placebo in 4 studies, and in one study there was a negative effect with treatment.

Adverse events: there was a broad spectrum of adverse events with the cholinesterase inhibitors, the most common being nausea, vomiting, diarrhoea and weight loss.

Authors’ conclusions
Recommendations for the use of cholinesterase inhibitors in the treatment of Alzheimer’s disease are questionable, owing to methodological flaws and small clinical benefits in the studies on which they are based.

CRD commentary
The review addressed a clear research question using defined inclusion criteria. Relevant databases were searched without language restrictions, although specific attempts to locate unpublished studies were not made. Studies might therefore have been missed. A detailed quality assessment of the studies was conducted, with appropriate measures taken to minimise error and bias. However, it was unclear whether such measures were used to minimise error and bias.
during the study selection and data extraction processes.

Relevant details of the individual studies were provided, though information on the study populations was limited. The narrative synthesis seemed appropriate given the focus of the review. The authors' conclusions follow from the evidence presented, although the review addressed global benefit and did not investigate the benefit to subgroups of individuals with Alzheimer's disease.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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